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31WHAT IS CLAIMED IS:

1. A thrombin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof:

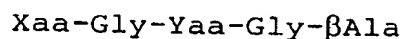


wherein

AS represents an S subsite blocking segment;

P represents a fibrinogen recognition exosite blocking segment; and

Z represents a S' subsite blocking segment which links AS and P, said S' subsite blocking segment having the following sequence:



wherein Xaa is a residue selected from the group of residue consisting of glycine, L-alanine, D-alanine, 2-aminoisobutyric acid, L- α -aminobutyric acid, D- α -aminobutyric acid, L-norvaline, D-norvaline, L-norleucine, D-norleucine, L-cysteine, L-penicillamine, D-penicillamine, L-methionine, D-methionine, L-valine, D-valine, L-tert-butylglycine, D-tert-butylglycine, L-isoleucine, D-isoleucine, L-leucine, D-leucine, cyclohexylglycine, L- β -cyclohexylalanine, D- β -cyclohexylalanine, L-phenylglycine, D-phenylglycine, L-phenylalanine, D-phenylalanine, L-homophenylalanine, D-homophenylalanine, L-histidine, D-histidine, L-tryptophan, D-tryptophan, L- β -(2-thienyl)-alanine, and D- β -(2-thienyl)-alanine;

Yaa is selected from the group of residue consisting of glycine, L-alanine, D-alanine, 2-aminoisobutyric acid, L- α -aminobutyric acid, D- α -aminobutyric acid, L-norvaline, D-norvaline, L-norleucine, D-norleucine, L-cysteine, L-penicillamine, D-penicillamine, L-methionine, D-methionine, L-valine, D-valine, L-tert-butylglycine, D-tert-butylglycine, L-isoleucine, D-isoleucine, L-leucine, D-leucine, cyclo-

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hexylglycine, L- β -cyclohexylalanine, D- β -cyclohexylalanine, L-phenylglycine, D-phenylglycine, L-phenylalanine, D-phenylalanine, homophenylalanine, histidine, L-tryptophan, D-tryptophan, L- β -(2-thienyl)-alanine, and D- β -(2-thienyl)-alanine.

2. The thrombin inhibitor of claim 1, wherein As has the following sequence:

Bbs-Arg-(D-Pip),

wherein Bbs and D-Pip represent 4-tert-butylbenzenesulfonyl and D-pipecolic acid, respectively.

3. The thrombin inhibitor of claim 1, wherein P has the following sequence:

Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH,

wherein Cha represent β -cyclohexyl-alanine.

4. The thrombin inhibitor of claim 2, wherein P has the following sequence:

Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH,

wherein Cha represent β -cyclohexyl-alanine.

5. The compound of claim 1, wherein said compound is selected from the group consisting of:

1) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Ala)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)

2) Bbs-Arg-(D-Pip)- α Abu-Gly-Gly-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)

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- 3) Bbs-Arg-(D-Pip)-Gly-Gly-(D- α Abu)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 4) Bbs-Arg-(D-Pip)-Nva-Gly-Gly-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 5) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Nva)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 6) Bbs-Arg-(D-Pip)-Nle-Gly-Gly-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 7) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Nle)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 8) Bbs-Arg-(D-Pip)-Met-Gly-Gly-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 9) Bbs-Arg-(D-Pip)-Val-Gly-Gly-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 10) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Val)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 11) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Tbg)-Gly- β Ala-Asp-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)

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- 12) Bbs-Arg-(D-Pip)-Ile-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 13) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Ile)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 14) Bbs-Arg-(D-Pip)-Leu-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 15) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Leu)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 16) Bbs-Arg-(D-Pip)-Chg-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 17) Bbs-Arg-(D-Pip)-Cha-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 18) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Phg)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 19) Bbs-Arg-(D-Pip)-Phe-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 20) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Phe)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)

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- 21) Bbs-Arg-(D-Pip)-Hph-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 22) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Hph)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 23) Bbs-Arg-(D-Pip)-His-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- and
- 24) Bbs-Arg-(D-Pip)-Thi-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH
(SEQ ID NO:3).

6. The compound of claim 1, wherein said compound is selected from the group consisting of:

- 1) Bbs-Arg-(D-Pip)-Nle-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)
- 2) Bbs-Arg-(D-Pip)-Gly-Gly-(D-Phg)-Gly- β Ala-Asp-
Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH;
(SEQ ID NO:3)

and

- 3) Bbs-Arg-(D-Pip)-Thi-Gly-Gly-Gly- β Ala-Asp-Tyr-
Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-(D-Glu)-OH
(SEQ ID NO:3).

7. Use of a compound as defined in claim 1 in the manufacture of a medicament for the treatment of vascular diseases in a mammal.

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8. The use of claim 7, wherein said mammal is a human.

9. A pharmaceutical composition for treating or preventing vascular disease, said composition comprising a therapeutically effective amount of a compound as defined in claim 1, and a pharmaceutically acceptable carrier.

10. A pharmaceutically acceptable combination for treating or preventing vascular disease in a mammal, comprising a compound as defined in claim 1, a thrombolytic agent and a pharmaceutically acceptable carrier.

11. The combination according to claim 10, wherein said thrombolytic agent is tissue plasminogen activator.

12. The combination according to claim 10, wherein said mammal is a human.

13. A method for the treatment or prevention of vascular diseases of a mammal comprising the administration of an effective amount of a composition according to claim 10.

14. The method according to claim 13, wherein said mammal is a human.

cl 7 *yes* on separate page